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TITLE

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The lessons from the Asilomar and the Napa meetings show how self-regulation and public deliberation can lead to regulation of new biotechnologies

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CRISPR-Cas9-based gene editing technology has fuelled a debate about the implications resulting from the new possibility of genome editing in the human germline [1,2]. Scientists have suggested how this technology could be regulated and evaluated to prevent misuse or abuse. Such discussions amongst scientists are not new: in the early days of recombinant DNA technology, scientists called attention to the potential benefits and risks of this new tool to genetically modifying living organisms. This development led to the famous conference held at Asilomar State Beach in California, in 1975. Forty years later, scientists and experts from ethics and law convened in Napa Valley, California, to discuss the scientific, societal and ethical implications of applying genome editing technologies in the human germline. The Napa group explicitly regarded their meeting as being in the tradition of Asilomar, to discuss guidelines and self-regulation for biotechnological developments.

Emerging technologies in biomedical research often touch on ethical and societal questions that cannot be answered by scientists alone. Thus, the inclusion of other experts in discussions about regulation as well as public engagement [3] has become increasingly important in order to take into account the wide spectrum of implications; and for maintaining public confidence in the regulatory instruments to control the use of novel technologies. Here, we discuss the opportunities and limitations of self-regulation for emerging biotechnologies based on a comparison of the Asilomar conference and the Napa meeting and propose a model that combines self-regulation with national and international governance in the context of using gene-editing technologies in the human germline.

From Asilomar to Napa

The paradigm case of scientific self-regulation in the biosciences is the above-mentioned "Asilomar Conference on Recombinant DNA," which was held after restriction enzymes and their application for genetically manipulating bacteria were discovered. Some molecular biologists, who at the time were concerned about the potential risks particularly for human health, convinced their colleagues to adhere to a voluntary moratorium on certain experiments until strategies to reduce such risks or prevent potential hazards were developed [4]. After many controversial debates before and during the conference, the attendees finally reached a consensus on safety issues and published recommendations on how to regulate this new technology. These recommendations formed the basis for the US National Institutes of Health's (NIH) "Guidelines for Research Involving Recombinant DNA Molecules" in the USA and subsequently influenced regulations in Europe. The Asilomar conference illustrates how the scientific community can effectively impose a moratorium on certain types of experiments and how a process of self-regulation in science can lead to guidelines for the safe handling of new biotechnologies. Given that the objective was to find *technical* solutions to address concerns about health risks, self-regulation seems reasonable, because scientists have expert knowledge pertaining to the potential risks and side effects of their research. The scientists did not, however, decide which risks were acceptable or not – this is not a scientific question, but a normative one.

Forty years after Asilomar, the scientific community convened again to discuss the risks of new biotechnological tools. This time, they are concerned with the CRISPR-Cas9 gene editing technology. The prospect of applying this technology to the human germline in particular raised concerns amongst scientists, non-scientific experts and the public. Unlike the modification of somatic cells, genome editing in germ cells or early embryos affects all cells of the developing individual and would then be passed on to future generations – this raises special health risks and ethical concerns. In January 2015, life scientists from the USA as well as experts from ethics and law convened in Napa Valley to discuss not only the scientific and medical, but also the legal and ethical implications of genomic editing in the human germline [2]. The Napa meeting – in contrast to the clear recommendations from the Asilomar conference – did not result in any specific guidelines. Nevertheless, the Napa group made several general recommendations for continuing the debate on genome editing in the human germline. They suggested, for instance, that the question of how to deal with potential risks for patients as well as societal and ethical implications should be discussed in an open and interdisciplinary dialogue [2]. They also discouraged pursuing clinical applications in humans

while discussions of the medical, societal, environmental and ethical implications were taking place [2] so as to provide time to formulate policies for regulation.

The Asilomar conference and the Napa meeting are two examples of how the scientific community can develop recommendations for applying and regulating emerging technologies. Obviously this involved individuals with varying opinions who had to find a minimal consensus for self-regulation that respects basic ethical and legal principles such as fundamental human rights. In the following, we will identify opportunities and limits of scientific self-regulation based on these two conferences.

The pros of self-regulation

There are some clear advantages to self-regulation. It raises scientists' awareness of their work's impact and clarifies their responsibilities. By starting an open and transparent process of building consensus, scientists draw public attention to a new development and its potential consequences for society and the environment and initiate and inform a public debate that may be followed by a political process of regulation. It is also beneficial for the scientific community itself, as it helps its members to understand the implications of their research and potential reactions from the public. Moreover, scientists show that they bear responsibility and that they do this in an open and transparent way.

The Asilomar conference showed that scientists are capable of reaching a consensus on controversial developments more quickly and effectively than a political process would allow, especially at the global level, as scientists share a common "language" and culture. In addition, they are well qualified to judge the potential risks and side effects of their work. Another advantage of the self-regulatory approach is that in light of new technological developments – which are not well-known among the broader public – scientists have the best insight to complement or revise self-regulatory guidelines.

The scientific system inherently has effective instruments and mechanisms for implementing guidelines and sanction violations. If journals, conferences, national academies and funding agencies insist on adherence to rules, it is in the scientists' own interest to comply as they all depend on these institutions for their work and careers. When a team of researchers from Sun Yat-sen University in Guangdong used the CRISPR-Cas9 technology to modify a disease-causing gene in human embryos, they restricted their experiment by using non-viable tri-

pronuclear zygotes [5]. However, even this self-restriction did not go far enough for *Nature* and *Science,* which both rejected their study [6]. Although the results were eventually published elsewhere [5], the initial rejections demonstrate the influence of journals on the conduct of research.

Although the Asilomar conference and the Napa meeting were driven by scientists from the USA, these opportunities suggest that a scientist-led approach to self-regulation could also be possible at a global level. The Declaration of Helsinki, first released in 1964 by the "World Medical Association"(WMA), is an example of self-regulation in the medical context. It defines basic ethical standards for research on human subjects that have been widely recognized by the medical community and have influenced national regulations in many countries.

Criticism of self-regulation

Despite these advantages, Asilomar and Napa have both encountered criticism, which reveals some disadvantages of consensus building and self-regulation. For instance, critics argued that the Asilomar conference was too narrowly focused on safety questions, disregarding urgent moral issues that may be raised by recombinant DNA technology. Both meetings were also criticized for excluding representatives from the general public [7,8]. This criticism reveals that consensus of scientists alone cannot be authoritative on controversial moral matters, such as the possibility of modifying the human germline, because they do not have any particular expertise for dealing with such moral and societal issues. In order to address moral questions raised by emerging technologies, experts from other fields such as ethics, law or social sciences need to be involved to analyse cultural, religious, ideological or emotional arguments. Moreover, their professional advice contributes to the decision-making process and consensus building. We would therefore call this approach of scientific self-regulation that includes other experts "self-regulation *plus*".

What would efficient global regulation in a scientific "self-regulation *plus*" framework look like? The process of reaching a minimal consensus for regulating an emerging technology needs to take place within a representative group of scientists. This could be initiated by a scientific institution that is acknowledged worldwide (such as the WMA for medical research). Alternatively, national academies could play a leading role as they already establish rules of good scientific practice and codes of conduct. Ideally, this "self-regulatory *plus*"

process should be accompanied by an open debate within the whole scientific community – for example through conference talks, open letters, commentaries or scientific papers.

A consensus-building process involving many different national academies could be a promising start for developing transnational and international guidelines, which should be binding for universities and other research institutions and influence the policies of national funding institutions. In addition, international scientific journals could publish only those articles based on the application of new technology that are in accordance with these guidelines. Besides the guidelines outlined by the Helsinki declaration another example of self-regulation is the standards of good scientific practice. Any self-regulatory system ultimately depends on the observance of guidelines and rules by scientists. As the scientific community is not a political body and thus has no legal power to govern research and its conduct, it may leave room for interpretation concerning what is in compliance and how to sanction misconduct. For this reason, the "self-regulatory *plus*" approach should not be understood as an alternative to political regulation, but as a fast, efficient and specific complement to it.

How then could a "self-regulatory *plus*" process be complemented by regulation or governance at the political and international level? International bodies and intergovernmental organs such as the United Nations, UNESCO or the WHO could serve as a framework for governance approaches, involving expert advice from scientists and/or by establishing international bodies with representatives from the scientific community. However, negotiations at an international policy level are often slow and inefficient: either the parties cannot agree on resulting documents or they reach a minimal consensus that is not sufficiently effective. For instance, it was not possible to reach a global consensus on a UN convention to ban human cloning; it was abandoned in favour of a less binding "UN Declaration on Human Cloning" that was only supported by 84 countries [9]. If, however, an agreement on the international governmental level should be reached, it will evidently be binding for scientists worldwide and might replace a self-regulatory framework (Fig 1).

The need for public deliberation

What role should the public play in the regulation of an emerging technology? If many different cultural, societal and religious values are touched upon – as in the case of genome editing in the human germline – the public must have a say on how these technologies should

be regulated and governed. However, involving the public at a global scale would be unmanageable – and values from different cultural and religious backgrounds would make it nearly impossible to reach any type of consensus. We therefore suggest that the public should be involved at the national level. For at least four reasons, scientific "self-regulation *plus*" must go hand-in-hand with national regulations that consider public concerns.

First, consensus building amongst scientists and other exerts lacks democratic legitimacy, as the public cannot vote on the decisions themselves or on who represents them during these discussions. Second, there is a significant risk that decisions made by an expert body will ignore some cultural, historical, religious and other societal values and principles. A participatory process, in which scientists engage with the public and which leads to recommendations for the regulation of the technology in question, could therefore help to develop national regulations that consider such issues. This points to a new role that academies could play at the national level: not only to represent scientists but also to mediate a dialogue between scientists and the general public.

Third, public trust and confidence in regulatory regimes is crucial for the successful regulation of emerging technologies. As scientists have a professional interest in using and developing these technologies, they might be suspected of giving more weight to their own preferences than to the common welfare. Thus it is easier to achieve trust in regulation through a public participatory approach. Fourth, a minimum consensus resulting from a scientific "self-regulation *plus*" process would be a compromise that may not go far enough for the public. National regulations can be more restrictive than a minimal consensus among scientists, as they incorporate public concerns and requests.

The current process initiated by the "International Summit on Human Gene Editing" held in Washington, DC, in December 2015, involves some elements of "self-regulation *plus*" that show how the scientific community builds consensus. The organizers of the summit – the "National Academy of Sciences" (NAS) and the "National Academy of Medicine" (NAM), along with the "Chinese Academy of Sciences" and the "Royal Society" of the UK – invited internationally-renowned life scientists, bioethicists and legal scientists to explore scientific, safety and ethical issues. The attendees concluded that, at the present stage, it would be irresponsible to proceed with the clinical use of the CRISPR-Cas9 technology in embryos without a better understanding of its risks and benefits, and without a broad agreement

(http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a). An experts' committee will therefore meet regularly and develop recommendations on how to deal with clinical, ethical, legal, and social implications of genome editing in the human germline.

The "International Summit on Human Gene Editing" adopts many of the elements that we discussed in our own approach to consensus-building and "self-regulation *plus*". However, the summit was organized by only four national academies; we believe that such a process should involve academies of more nations. This would not only be a better representation of the global scientific community, but there would also be a higher chance that the guidelines will be implemented by journals, funding agencies, universities and other scientific institutions around the globe.

Transparency and trust building

What specific points must be taken into account for the implementation of "self-regulation *plus*" in case of human gene-editing technology? During the forty years since the Asilomar conference, the environment in which research takes place has changed profoundly. Debates over emerging biotechnologies and their application take place in a public arena accompanied by intense media interest. The process initiated by the Asilomar conference cannot therefore be transferred on a one-to-one basis to regulate today's technologies. Ethical aspects, which require the inclusion of ethicists and lawyers, have to be considered at an early stage. Self-regulation and its guiding principles must also be flexible enough to adapt to rapid developments in the global scientific community. As discussed above, "self-regulation *plus*" alone is therefore not sufficient to govern emerging biotechnologies, but it would be suitable to initiate the debate on regulations and governance from within the scientific community.

Self-regulation in the scientific community only works effectively as long as the public trusts scientists to serve the public interest. Thus, it is essential that the consensus building process amongst scientists and other experts is transparent. In consequence, this process should be covered by the media. Moreover, a public debate should offer the opportunity for scientists to address public reactions to and concerns about the consensus-building process. There should be open and mutual exchange between scientists and the public through open conferences, public hearings, the media and the Internet. Another reason why transparency and openness is crucial is that the commercialization of science has resulted in an increasing number of

conflicts of interest. As stressed by Paul Berg, unlike in the 1970s, many scientists today work for private companies [10]. Therefore, scientists have to show convincingly that their self-regulation is not driven by third-party interests.

"Self-regulation *plus*" is a fast, specific and effective way of providing a basic level of regulation that raises the awareness of these issues, both within the scientific community and beyond. For this reason, it is important that the global scientific community assumes responsibility for emerging developments such as CRISPR-Cas9 technology by paying attention to a self-regulatory approach and refine it to the next level.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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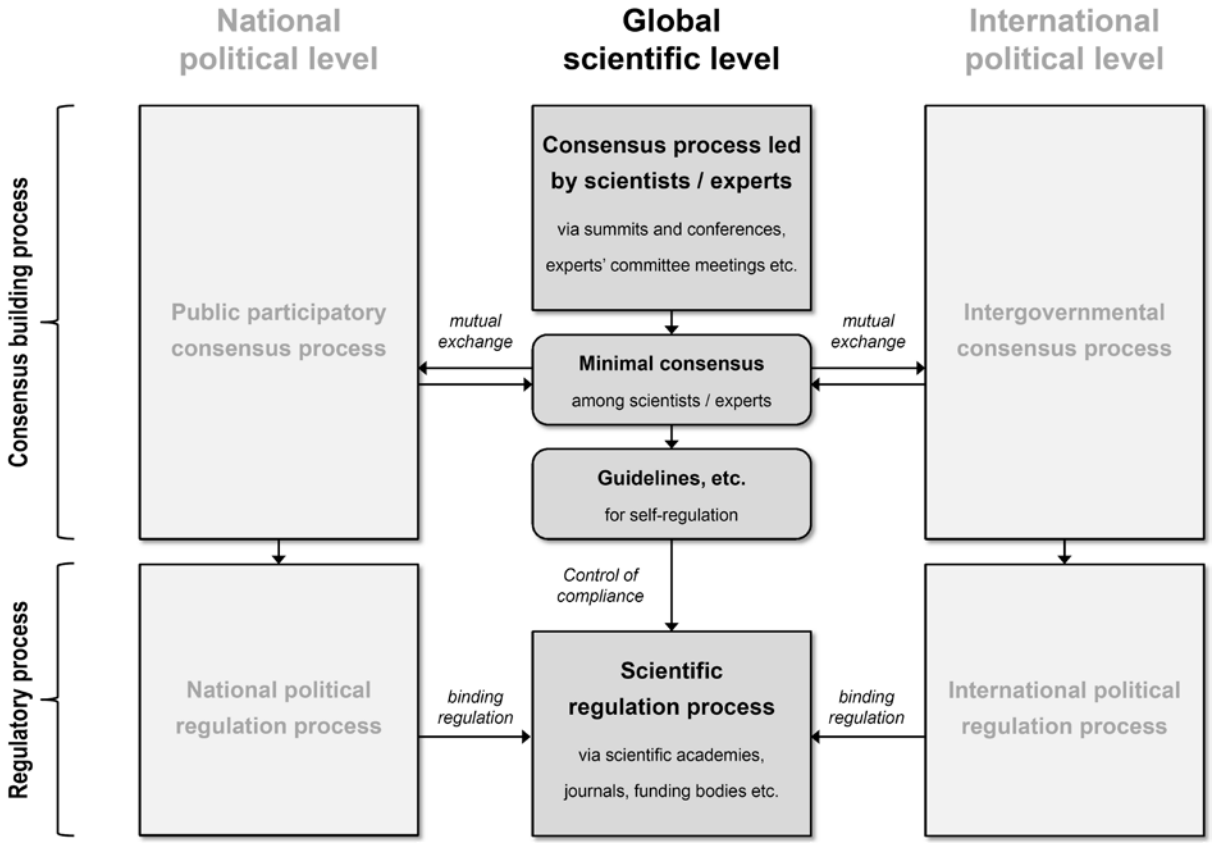

Fig 1 | Different approaches for consensus-building and regulation, focusing on the self-regulation of the scientific community on a global level